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Application No.: 10/523328

Docket No.: WYTH-P01-001

Reply to Notice of Noncompliant Amendment dated January 16, 2009

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

Listing of Claims

1. (Currently amended) An isolated, purified, or recombinant protein complex comprising at least the following three polypeptides:
 - (i) a tumor necrosis factor alpha (TNF- α) polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 1, or a functional variant thereof;
 - (ii) a TNF- α receptor (TNFR) polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 3 or 5, or a functional variant thereof; and
 - (iii) ~~at least one polypeptide selected from the group consisting of: NF- κ B activating kinase (NAK), RasGAP3, a TRCP1 polypeptide[[,]] TRCP2~~ which has an amino acid sequence at least 95% identical to SEQ ID NO: 17, or and a functional variant thereof.
2. (Original) The complex of claim 1, wherein the TNFR polypeptide is a TNFR1 or TNFR2 polypeptide.
3. (Withdrawn, currently amended) The complex of claim 1, further comprising a TNF- α polypeptide, a TNFR polypeptide and a NAK polypeptide at least one polypeptide selected from: (a) a RasGAP3 polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 15, or a functional variant thereof; (b) an NF- κ B activating kinase (NAK) polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 13, or a functional variant thereof; and (c) a TRCP2 polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 19, or a functional variant thereof.
4. (Withdrawn, currently amended) The complex of claim [[1]]3, comprising a TNF- α polypeptide, a TNFR polypeptide, the TRCP1 polypeptide, and a RasGAP3 polypeptide.
5. (Currently amended) The complex of claim [[1]]3, comprising [[a]] the TNF- α polypeptide, [[a]] the TNFR polypeptide, and [[a]] the TRCP1 polypeptide, and the NAK polypeptide.

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6. (Withdrawn, currently amended) The complex of claim [[1]] 3, comprising [[a]] the TNF- α polypeptide, [[a]] the TNFR polypeptide, the TRCP1 polypeptide, and [[a]] the TRCP2 polypeptide.
7. (Withdrawn, currently amended) The complex of claim [[1]] 3, comprising [[a]] the TNF- α polypeptide, [[a]] the NAK polypeptide, and [[a]] the TNFR1 polypeptide, the TRCP1 polypeptide, the RasGAP3 polypeptide, and the TRCP2 polypeptide.
8. (Currently Amended) The complex of claim 1, further comprising at least one polypeptide selected from ~~the group consisting of~~: TRADD, TRAF2, TRAP2 and a functional variant thereof.
9. (Withdrawn, currently amended) The complex of claim 8, comprising [[a]] the TNF- α polypeptide, the TRCP1 polypeptide, [[a]] the NAK polypeptide, [[a]] the TNFR1 polypeptide, [[a]] the TRAF2 polypeptide, and [[a]] the TRADD polypeptide.
10. (Withdrawn, currently amended) The complex of claim 8, comprising [[a]] the TNF- α polypeptide, [[a]] the TNFR polypeptide, [[a]] the NAK polypeptide, [[a]] the RasGAP3 polypeptide, [[a]] the TRCP1 polypeptide, [[a]] the TRCP2 polypeptide, [[a]] the TRADD polypeptide, [[a]] the TRAF2 polypeptide, and [[a]] the TRAP2 polypeptide.
11. (Original) The complex of claim 1, wherein said TNF- α is a fusion protein.
12. (Original) The complex of claim 1, wherein said TNFR is a fusion protein.
- 13-16. (Canceled)
17. (Currently amended) An isolated, purified, or recombinant protein complex comprising:
 - (i) a TNF- α receptor (TNFR) polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 3 or 5, or a functional variant thereof; and

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- (ii) ~~at least one polypeptide selected from the group consisting of:~~ an NF- κ B activating kinase (NAK) polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 13, or a functional variant thereof[.];
- (iii) a RasGAP3 polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 15, or a functional variant thereof[.];
- (iv) a TRCP1 polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 17, or a functional variant thereof[.]; and
- (v) a TRCP2 polypeptide which has an amino acid sequence at least 95% identical to SEQ ID NO: 19, or ~~and~~ a functional variant thereof.

18-21. (Canceled)

22. (Original) The complex of claim 17, wherein said TNFR polypeptide is a TNFR1 polypeptide or a TNFR2 polypeptide.
23. (Currently Amended) The complex of claim 17, further comprising at least one polypeptide selected from ~~the group consisting of:~~ TNF- α , TRADD, TRAF2, and TRAP2.
24. (Withdrawn, currently amended) The complex of claim 23, comprising ~~the~~ [[a]] the TNF- α polypeptide, ~~the~~ [[a]] the TNFR1 polypeptide, ~~the~~ [[a]] the NAK polypeptide, ~~the~~ [[a]] the RasGAP3 polypeptide, ~~the~~ [[a]] the TRCP1 polypeptide, ~~the~~ [[a]] the TRCP2 polypeptide, ~~the~~ [[a]] the TRADD polypeptide, ~~the~~ [[a]] the TRAF2 polypeptide, and ~~the~~ [[a]] the TRAP2 polypeptide.
25. (Original) The complex of claim 17, wherein said TNFR polypeptide is a fusion protein.

26-32. (Canceled)

33. (Withdrawn) A host cell comprising a first nucleic acid, a second nucleic acid and a third nucleic acid, wherein the first nucleic acid comprises a recombinant nucleic acid encoding a

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TNF- α polypeptide, wherein the second nucleic acid comprises a recombinant nucleic acid encoding a TNFR polypeptide and wherein the third nucleic acid comprises a recombinant nucleic acid encoding a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2.

34. (Withdrawn) The host cell of claim 33, wherein the first nucleic acid comprises a recombinant nucleic acid encoding a TNF- α polypeptide, wherein the second nucleic acid comprises a recombinant nucleic acid encoding a TNFR1 polypeptide and wherein the third nucleic acid comprises a recombinant nucleic acid encoding a NAK polypeptide.
35. (Withdrawn) A host cell comprising a first nucleic acid and a second nucleic acid, wherein the first nucleic acid comprises a recombinant nucleic acid encoding a TNFR, and wherein the second nucleic acid comprises a recombinant nucleic acid encoding a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2.
36. (Withdrawn) The host cell of claim 35, wherein the first nucleic acid comprises a recombinant nucleic acid encoding a TNFR1 polypeptide and wherein the second nucleic acid comprises a recombinant nucleic acid encoding a NAK polypeptide.
37. (Withdrawn) An assay for identifying a test compound which inhibits or potentiates the stability of a complex, comprising:
- (a) forming a reaction mixture including:
 - (i) a TNF- α polypeptide;
 - (ii) a TNFR polypeptide;
 - (iii) at least one polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2; and
 - (iv) a test compound; and
 - (b) detecting the presence of TNF- α or TNFR in the complex;

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wherein a change in the presence of TNF- α or TNFR in the complex in the presence of the test compound, relative to the presence of TNF- α or TNFR in the complex in the absence of the test compound, indicates that said test compound potentiates or inhibits the stability of said complex.

38. (Canceled)

39. (Withdrawn) An assay for identifying a test compound which inhibits or potentiates the stability of a complex, comprising:

(a) forming a reaction mixture including:

(i) a TNFR polypeptide;

(ii) at least one polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2; and

(iii) a test compound; and

(b) detecting the association between the TNFR and a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2;

wherein a change in the association between TNFR and a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2 in the presence of the test compound, relative to the association between TNFR and a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2 in the absence of the test compound, indicates that said test compound potentiates or inhibits the stability of said complex.

40-43. (Canceled)

44. (Withdrawn) A method for modulating, in a cell, a protein complex comprising at least a first protein and a second protein, wherein said first protein is TNFR, and wherein said second protein is selected from the group consisting of: NAK, RasGAP3, TRCP1, and

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TRCP2, said method comprising: administering to said cell a compound capable of modulating said protein complex.

45. (Withdrawn) The method of claim 44, wherein the protein complex further comprises TNF- α .
46. (Withdrawn) A method of producing a functional complex comprising:
- (i) transfecting a cell with a polynucleotide encoding a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2;
 - (ii) contacting said cell with a TNF- α polypeptide;
 - (iii) thereby forming a complex.
47. (Withdrawn) The method of claim 46, further comprising a TNFR polypeptide.
48. (Withdrawn) A method for treating a TNF- α -related disorder, by administering an effective amount of a compound that inhibits the interaction of TNF- α or TNFR with a polypeptide selected from the group consisting of: NAK, RasGAP3, TRCP1, and TRCP2.
49. (Withdrawn) The method of claim 48, wherein said compound is selected from the group consisting of: a small molecule, an antibody, and a peptide.
50. (Withdrawn) A method of identifying a test compound that is a candidate modulator of inflammation or apoptosis, the method comprising:
- (i) forming a mixture comprising a TRCP1 polypeptide or a variant polypeptide thereof, and a test compound; and
 - (ii) measuring the interaction between the TRCP1 polypeptide or the variant and the test compound;

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wherein a test compound that interacts with the TRCP1 polypeptide or functional variant is a candidate modulator of inflammation or apoptosis.

51. (Withdrawn) The method of claim 50, wherein (i) comprises forming the mixture in vitro.
52. (Withdrawn) The method of claim 50, wherein (i) comprises contacting a cell expressing a TRCP1 polypeptide or a variant thereof, with the test compound.
53. (Withdrawn) A method of identifying a test compound that is a candidate modulator of inflammation or apoptosis, the method comprising:
 - (i) forming a mixture comprising a TRCP2 polypeptide or a variant polypeptide thereof, and a test compound; and
 - (ii) measuring the interaction between the TRCP2 polypeptide or the variant and the test compound;

wherein a test compound that interacts with the TRCP2 polypeptide or functional variant is a candidate modulator of inflammation or apoptosis.

54. (Withdrawn) The method of claim 53, wherein (i) comprises forming the mixture in vitro.
55. (Withdrawn) The method of claim 53, wherein (i) comprises contacting a cell expressing a TRCP2 polypeptide or a variant thereof, with the test compound.
56. (Withdrawn) A method of treating a TNF- α -related disease which includes an inflammatory or apoptotic component, by administering an effective amount of a therapeutic composition that modulates TRCP1 or TRCP2.
57. (Canceled)

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